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5487	7590	06/10/2009	EXAMINER	
ANDREA Q. RYAN			GOON, SCARLETT Y	
SANOFI-AVENTIS U.S. LLC			ART UNIT	
1041 ROUTE 202-206			PAPER NUMBER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/734,573	FRICK ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 13 April 2009.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-7 and 9-12 is/are pending in the application.
 4a) Of the above claim(s) 9-12 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-7 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1.) Certified copies of the priority documents have been received.
 2.) Certified copies of the priority documents have been received in Application No. _____.
 3.) Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____. | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 13 April 2009.

Claims 1-7 and 9-12 are currently pending in the instant application.

Claims 9-12 are withdrawn pursuant to a restriction requirement.

Claims 1-7 will be examined on its merits herein.

Priority

This application claims priority to U.S. provisional application no. 60/466449 filed on 29 April 2003, German foreign application 10258008.1-43 filed on 12 December 2002, and PCT/EP03/13455 filed on 28 November 2003. A certified copy of foreign priority document 10258008.1-43 in German has been received. An English translation of the German priority document as well as a statement verifying the accuracy of the translation was received by the Office on 22 April 2009.

Rejections Withdrawn

Applicants' Amendment, filed 13 April 2009, with respect to the rejection of claims 1-7 on the ground of nonstatutory doubling patenting over claims 1-10 and 15 of copending Application no. 11/567,410, has been fully considered and is persuasive because the amended claim limits R7 to linear chains whereas the copending application requires that Cyc2 be a 5- to 7-membered ring.

These rejections have been **withdrawn**.

Applicant's amendment, filed 13 April 2009, with respect to the rejections of claims 1-7 under 35 USC § 112, first paragraph, for scope of enablement, has been fully considered and is persuasive because the claims have been amended to more accurately claim subject matter as enabled by the Specification.

These rejections have been **withdrawn**.

The following rejections of record in the previous Office Action are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/036602 to Ohsumi *et al.* (IDS dated 5 March 2004; U.S. Patent No. 6,815,428 B2 used as English equivalent), in view of journal publication by Díez-Sampedro *et al.* (of record).

Ohsumi *et al.* teach pyrazole-O-glycoside derivatives represented by formulas (1A) and (1B) for use as a diabetic medicine (abstract; column 1, lines 55-67; column 2, lines 1-14; claim 1). Exemplary compounds 1-16 are also shown (columns 31-35).

Pharmaceutical compositions comprising the aforementioned compounds inhibit the Na^+ -dependent glucose transporter (SGLT), which reduces renal glucose reabsorption at renal uriniferous tubules (column 1, lines 15-18 and lines 37-40). As a result, the level of blood sugar decreases. SGLT-1 and SGLT-2 are known membrane proteins which transport glucose.

Ohsumi *et al.* do not teach pyrazole-O-glycoside derivatives wherein the C-4 hydroxyl is substituted with a fluorine atom.

Díez-Sampedro *et al.* teach the effects of varying the hydroxyl groups on the glucose ring and its recognition by the Na^+ -dependent glucose transporter (SGLT1). SGLT1 is highly selective for its natural substrates, D-glucose and D-galactose (abstract). Díez-Sampedro *et al.* individually substituted the different hydroxyl groups on the glucose ring with a hydrogen, fluorine or methyl group and studied the ability of SGLT1 in recognizing and binding the modified substrate (p. 49189, column 1, subsection "Compounds"; p. 49189, column 2, full paragraphs 3-5). The only increase in the apparent affinity, compared with glucose, was found when the equatorial hydroxyl group in the fourth position was replaced with a fluorine atom (4F4DOglc) where the $K_{0.5}=0.07\text{mM}$ (p. 49189, column 2, fifth full paragraph). Since 4F4DOglc had a lower $K_{0.5}$ compared with glucose (six times higher affinity), Díez-Sampedro *et al.* concluded that the hydrogen bond donation of the fourth position of glucose was detrimental to sugar binding (p. 49192, column 1, third full paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ohsumi *et al.* patent, regarding pyrazole-O-

glycoside derivatives that inhibit the Na^+ -dependent glucose transporter (SGLT) for use as a diabetic medicine, with the teachings of Díez-Sampedro *et al.*, regarding the increased apparent affinity of 4F4DOglc by SGLT as compared with the native glucose substrate. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Díez-Sampedro *et al.*, that SGLT has a higher apparent affinity for the glucose substrate when the 4-hydroxyl group is replaced with a fluorine atom. A medicinal chemist would view that a compound with an increased apparent affinity for a receptor, as in the situation described by Díez-Sampedro *et al.*, can likely serve as an inhibitor of the substrate, and would thus have been motivated to synthesize such a compound as inhibitors of SGLT can be used as a diabetic medicine.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 13 April 2009 with respect to the rejection of claims 1-7 made under 35 USC § 103(a) as being unpatentable over Ohsumi *et al.* in view of Díez-Sampedro *et al.*, have been fully considered but they are not persuasive.

Applicants are requested to note that U.S. Patent No. 6,815,428 B2 to Ohsumi *et al.* claims priority to WIPO publication WO 2002/036602 and that in view of the filed English translation of the German priority document, the rejection of the previous Office Action has been amended as indicated above such that the claims are unpatentable over the earlier filed WIPO document published by Ohsumi *et al.* As the WIPO

publication and U.S. patent are directed to the same subject matter, and the U.S. patent is used as the English equivalent of the WIPO publication, no changes to the rejection of record are made.

Applicants argue that the Díez-Sampedro *et al.* reference represents a "teaching away" inasmuch as it was known in the art (e.g. Ellsworth *et al.* of WO 01/27128) that inhibition of SLT-1 is undesirable due to predicted severe side effects. This argument is not persuasive because Ellsworth *et al.* only teaches that "[i]nhibition of SGLT1 could also have serious adverse consequences". Thus, as Ellsworth *et al.* do not definitively teach that inhibition of SGLT1 would necessarily result in adverse consequences, it is considered that one of ordinary skill in the art familiar with the teachings of Ohsumi *et al.* and Díez-Sampedro *et al.* would be motivated to combine the teachings and replace the 4-OH group of the compounds disclosed by Ohsumi *et al.* with a fluoro group in order to increase its apparent affinity for SGLT, as suggested Díez-Sampedro *et al.*, and thus produce a SGLT1 inhibitor that could be used as a diabetic medicine. Furthermore, Ellsworth *et al.* teach that the possible adverse consequences of inhibition of SGLT1 is a result of "mutations in the SGLT1 cotransporter," and do not teach that it is due to the direct inhibition of SGLT1. One of ordinary skill in the art is aware that receptor inhibition can result in different downstream effects depending on the structure of the compound and its mechanism of action. Thus, in the absence of any definitive teaching that inhibition of SGLT1 is detrimental, Ellsworth *et al.* would not necessarily "teach away" the combined teachings of Ohsumi *et al.* and Díez-Sampedro *et al.* Thus, the

claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

The rejection is still deemed proper and therefore adhered to.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
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/SCARLETT GOON/
Examiner
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